

Pan-retinal photocoagulation and other forms of laser treatment and drug therapies for non-proliferative diabetic retinopathy: systematic review and economic evaluation

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Scientific summary

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Background

The commissioning brief asked:

What is the clinical effectiveness and cost-effectiveness of pan-retinal laser treatment in the management of non-proliferative (pre-proliferative) diabetic retinopathy (NPDR)?

A review of clinical guidelines showed that treatment at the NPDR stage is currently either not recommended or recommended only in certain circumstances.

Decision problem

With the agreement of the Health Technology Assessment (HTA) programme, we extended the question in the commissioning brief in two ways. Firstly, there have been developments in methods of laser photocoagulation. So if the evidence supported pan-retinal photocoagulation (PRP) at the NPDR stage, one question would be which form of laser treatment would be used. Secondly, there have been advances in drug treatment with the arrival of the anti-vascular endothelial growth factor (VEGF) drugs. Our scoping searches showed that they were being used in combination with laser treatment to reduce adverse effects, and so we include a review of such combinations.

So the decision problem becomes:

- Would it be worthwhile to intervene with PRP earlier in diabetic retinopathy (DR), at the severe NPDR stage, rather than wait till the high-risk proliferative diabetic retinopathy (HR-PDR) stage? Treating at early PDR stage would be another option.
- If so, what form of laser treatment should be used?
- Are drug-PRP combinations clinically effective and cost-effective?

Note that the review is not concerned with the effectiveness of laser treatment of diabetic macular oedema (DMO), which is done with focal or grid laser.

Methods

Systematic reviews of the trial evidence on:

- treatment at NPDR stage versus waiting till PDR develops
- the relative effectiveness and safety of newer versus conventional laser methods
- the effectiveness of anti-VEGF drugs and injected steroid in combination with PRP.

This was supplemented by evidence on adverse effects from other types of study.

Review of previous economic studies. Construction of an economic model and cost-effectiveness analysis.

Results

Evidence on the timing of PRP came almost entirely from the Early Treatment Diabetic Retinopathy Study (ETDRS). This was a large high-quality study that recruited patients with moderate to severe NPDR or early PDR, with or without macular oedema (MO), in the years 1980 to 1985. Patients were randomised to immediate PRP ('early photocoagulation') or to observation and PRP at the HR-PDR stage ('deferred photocoagulation'). Those with no MO were further randomised to different intensities of PRP, known as full or mild scatter. Those with MO randomised to early photocoagulation were further randomised to either full or mild scatter, and to early or delayed focal laser treatment for the DMO.

There were three groups of eyes in ETDRS:

- Category 1 Moderate to severe NPDR or early PDR but no MO.
- Category 2 Mild to moderate NPDR ('less severe retinopathy') and MO.
- Category 3 Severe NPDR or early PDR ('more severe retinopathy') and MO.

The primary end point of the ETDRS was the development of severe visual loss (SVL). The absolute risks of SVL in the trial were low: 2.6% with early laser and 3.7% with deferred PRP. The 5-year relative risk (RR) of SVL for eyes assigned to early photocoagulation compared with deferral was 0.77 [99% confidence interval (CI) 0.56 to 1.06]. So early photocoagulation reduces the risk of SVL by about 23%, though the 99% CI levels overlapped with no difference.

The RRs for the three categories differed:

- Category 1 = 1.37 (99% CI 0.67 to 2.77).
- Category 2 = 0.59 (99% CI 0.32 to 1.09).
- Category 3 = 0.70 (99% CI 0.44 to 1.11).

Compared with deferral of photocoagulation, early photocoagulation reduced progression to HR-PDR in each baseline category. Full scatter reduced progression to HR-PDR by 50% and mild scatter by 25% compared with the deferred group.

By 5 years, 3.9% in the deferred group and 2.2% in the early group had undergone vitrectomy. The indications for vitrectomy were either vitreous haemorrhage (53.9%) or retinal detachment with or without vitreous haemorrhage (46.1%).

The RR of the combined end point of SVL or vitrectomy for eyes assigned to early photocoagulation compared with eyes assigned to deferred photocoagulation was statistically significant at 0.67 (99% CI 0.52 to 0.87).

One harm associated with early PRP was early moderate visual loss, shown more frequently at 6 weeks and 4 months than with eyes assigned to deferral; however, there was no difference at 3-year follow-up.

The ETDRS found that the benefits of early PRP were greater in patients with type 2 diabetes than in those with type 1, though this may have been a chance finding.

The conclusions of the authors of the study were cautious, leaving some uncertainty regarding PRP at the severe NPDR stage:

Provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate non-proliferative retinopathy. When retinopathy is more severe, scatter photocoagulation should be considered and usually should not be delayed if the eye has reached the high-risk proliferative stage.

Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology 1991;98:766–85.9

The evidence from ETDRS suggests that treatment of severe NPDR and early PDR was more effective – though the 99% CIs were wide – in reducing future visual loss, than waiting to treat at HR-PDR stage, but ETDRS did not provide results separately for severe NPDR and early PDR. The primary end point, SVL [defined as visual acuity (VA) < 5/200 at two consecutive follow-up visits 4 months apart], was very severe. The observed reduction in HR-PDR might have been expected to lead to further reductions in visual loss with longer follow-up.

Types of laser

We included only studies published since 2000, in order to reflect current practice, and we included studies at any stage of retinopathy because of a dearth of laser studies at NPDR stage. For effectiveness in terms of visual state, we preferred a minimum duration of 6 months, but we included trials with shorter follow-up, because regression of neovascularisation can be seen 2–3 months after PRP. We also included non-trial studies of shorter duration for data on adverse effects.

We found 12 randomised controlled trials (RCTs), generally of good quality, but often with small numbers of patients. The majority of the patients had PDR, with a few with very severe NPDR.

The types of laser, and method of use, varied considerably amongst studies. Newer lasers can do a number of burns at the same time, known as pattern or multi-spot, which reduces the time required for PRP. However, other variations include the type of laser and wave length used (for instance argon vs. diode; 810-nm vs. 532-nm wave length; whether micropulse technology is used), and the parameters that can be changed when actually applying the laser (power, which can be decreased to ‘sub-threshold’ levels or increased to achieve ‘light’ or more ‘marked’ burns; spot size; duration of the laser burn).

There were three trials of multi-spot or pattern photocoagulation against single-spot argon PRP, with a total of 280 eyes treated. Pattern photocoagulation appeared to be as effective but with fewer adverse effects.

Other studies examined different ways of giving standard PRP, some suggesting that lighter burns PRP with conventional lasers gave similar effectiveness but fewer adverse effects than more intense burns. None of the studies showed a significant difference amongst the lasers in terms of change in VA.

The Japanese approach of selective PRP aimed at ischaemic areas only in pre-proliferative diabetic retinopathy (PPDR) (their term, presumably severe NPDR) delayed progression to PDR, with only 15% of the selective group developing PDR compared with 52% of those receiving no photocoagulation ($p = 0.03$). The rationale is that it is the ischaemic areas that produce VEGF, and treating only those saves some peripheral vision.

In summary, recent evidence has shown a trend towards ‘lighter’ photocoagulation, with reduced intensity of laser burns, but, in most studies, without loss of effectiveness. It is worth noticing that lighter photocoagulation can be given with argon machines.

Data on adverse events come from both RCTs and non-randomised studies, with a mixture of different types of lasers and different methods of photocoagulation, different levels of severity of DR, different follow-up times, and different methods of measuring outcomes.

Pan-retinal photocoagulation destroys retinal tissue and this can lead to symptoms due to the loss of function of the burned areas, including peripheral visual field defects, reduced night vision, reduced colour vision and decreased contrast sensitivity. Visual field defects can occur in up to 50% of treated patients, depending on intensity of PRP and level of testing. However, it does help preserve the more important central vision.

The most important adverse effect associated with PRP is MO, which can lead to a reduction in VA, mostly in the short term, though in one of the older trials, persistent VA losses were attributed to treatment, of one line in 11% and two or more lines in an additional 3%, on the Snellen chart.

In older studies such as ETDRS, which were carried out before optical coherence tomography (OCT) became available, some patients may have had undiagnosed MO at baseline, which was exacerbated rather than caused by PRP. With better detection of MO, focal laser treatment or anti-VEGF therapy can be given before PRP to reduce the risk, with choice of treatment being based on retinal thickness, as per National Institute for Health and Care Excellence guidelines. Because of the risk of precipitating MO, conventional argon laser photocoagulation is usually given over several sessions. There is some evidence that the risk is less with modern laser technologies.

It appears that pattern scan lasers are now standard for PRP, with single-spot argon lasers being replaced.

The conclusion from the review of recent laser studies is that there have been advances in laser technologies but no convincing evidence as yet that modern lasers are more effective than the argon laser used in ETDRS.

Drug and laser combinations

We reviewed studies of the efficacy of drug and laser combination in patients with NPDR or PDR. The main interest was reduction in adverse effects, and in particular PRP-associated MO.

Eleven trials compared the efficacy of anti-VEGFs or steroids used in conjunction with PRP. Seven studies used the anti-VEGFs ranibizumab or bevacizumab, and six were of triamcinolone (two trials included both an anti-VEGF drug and a steroid). Five studies included some patients with NPDR. Most trials had small numbers of patients and were short term but that should not be a problem because the MO provoked by PRP occurs soon after PRP.

For the anti-VEGF drugs the evidence is fairly consistent – a single injection appears to reduce the risk of PRP-induced MO.

In three trials, intravitreal triamcinolone (IVTA) reduced the risk of MO after PRP and improved best corrected visual acuity (BCVA) in patients with clinically significant macular oedema (CSMO), but in another it did not. However, IVTA increased intraocular pressure (IOP), a well-known side effect of steroids. One trial of a single sub-Tenon's capsule injection of triamcinolone before PRP showed benefit in preventing visual loss at 6 months, without increasing IOP. Given the higher risk of adverse effects, anti-VEGF treatment might be preferable to steroids, though cost would need to be considered. Triamcinolone is not licensed for use in the eye.

Overall, adjuvant anti-VEGF or triamcinolone treatment reduced the adverse effects of PRP. The strength of the evidence base is that we have a set of RCTs. The limitations are their small size, and, for our purposes, that most patients had HR-PDR rather than severe NPDR. We also need more data on the value of anti-VEGF treatment for different patterns of MO, such as foveal and extra-foveal.

One implication of modern laser methods and the use of anti-VEGF or steroid drugs may be a reduction in the risk of DMO when PRP is given in one session.

Cost-effectiveness

We carried out a systematic review of previous economic evaluations on the use of PRP, with or without adjuvant anti-VEGF drugs or steroid. A broad search was done in MEDLINE, EMBASE and Web of Science, and included meetings abstracts.

Studies were considered relevant to this review if they met the following inclusion criteria:

- full economic analysis on the treatment (laser and/or medication) for DR, *or*
- partial economic analysis (costs or effects) on the treatment (laser and/or medication) for DR (e.g. costing studies or quality-of-life studies).

We checked 1896 abstracts. Five studies provided partial economics analyses. No studies provided a full economic evaluation. However, many abstracts provide useful data on adverse events, disutilities and patient preferences.

We constructed a Markov model, starting with a cohort of people with moderate NPDR who could progress through all the stages of retinopathy to SVL. The model had two treatment arms:

1. *Current practice*. Patients are observed until they progress to the HR-PDR health state (or later) when they receive PRP.
2. *Early PRP (intervention)*. Patients receive PRP once they progress to the severe NPDR health state, or at the early PDR stage.

For the base case, we used the data from the ETDRS trial, which is the only one that addresses the timing question. The results indicate that early PRP could be more effective and less costly than delayed PRP.

There have been developments since the landmark ETDRS trial, including those mentioned above: advanced laser technologies, more accurate diagnosis of MO using OCT, and reduction in the risk of PRP-associated MO by adjuvant drug treatment. We therefore carried out sensitivity analyses to take account of these but the results were similar.

Limitations in the economics analysis include the wide CIs in the ETDRS, differences in results by type of diabetes, and uncertainties with progression rates, but the main one is the lack of a trial of early versus deferred PRP with modern laser techniques and adjuvant drug treatment.

Not everyone with severe NPDR would progress to HR-PDR, so treatment of severe NPDR might mean treating some people who might not benefit.

Research needs

For the key question of timing of PRP, we are dependent on the ETDRS, which did not provide results separately for severe NPDR and early PDR, and in which the reduction in SVL did not quite reach statistical significance, albeit using 99% CIs. Our view is that the current evidence base is insufficient to recommend a policy of PRP at the severe NPDR stage, and that a trial is necessary.

Since the ETDRS, the balance of benefits and harms may have changed. The side effects of PRP may be less than those observed at the time of the ETDRS, given newer laser technologies and modes of treatment, better identification of subclinical DMO using new imaging technologies such as OCT, and new treatment options for preventing or treatment PRP-induced DMO.

The use of adjuvant anti-VEGF or short-acting steroid drugs may further reduce the harms, perhaps allowing lighter laser and fewer burns.

The trial would compare 'best' PRP at severe and very severe NPDR stage versus the same PRP regimen delayed till HR-PDR develops. It would use pattern laser systems. There might be three arms: severe and very severe NPDR, early PDR, and HR-PDR. A further randomisation could examine the value of anti-VEGF drugs in reducing adverse effects.

Outcomes would include preservation of central vision, and also peripheral vision and driving standards. Loss of ability to drive is important to patients.

Conclusions

The current evidence is insufficient to recommend that PRP be used at the non-proliferative stage of DR.

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